Using Chinese natural products for diabetes mellitus drug discovery and development

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Abstract:
This paper provides a review of natural Chinese drug products, including phytochemic compounds, medicinal herbs and multi-component herbal formulae, that have been reported to possess hypoglycemic activity with mechanisms for antidiabetic action. Along with a great number of combination formulae, — 187 different Chinese medicinal herbs are clinically applied to treat diabetes mellitus and its complications in China, most of which have achieved reasonably good clinical outcomes. These valuable data and practical experience provide a promising opportunity for the discovery and development of drug candidates with good therapeutic efficacy and low toxicity. The concept of treating complex, multifactorial metabolic diseases, such as diabetes, using multi-component therapeutics, including single-herb formulae and combination herbal formulae, shall be regarded as a concerted pharmacologic intervention of multiple compounds interacting with multiple targets and possessing interdependent activities that are required for a synergistic or optimal effect. The conventional approach for the discovery and development of antidiabetic drug products from natural products involving a high-throughput, bioactivity guided drug screening of single compounds obtained from thousands of herbs has proven to be a costly and non-productive effort. Hence, an alternative way of developing new drug candidates, as suggested in this review, is to reduce and simplify a well-established combination herbal formula, along with the pharmacologic evaluation of a small group of phytochemic compounds, which are therapeutically effective as the original formula and have known chemical structures, compositions and mechanisms of action that are similar to chemical drugs.

Keywords: combination herbal formulae, diabetes mellitus, multi-component therapeutics, traditional Chinese medicine

Article:

1. Introduction

According to its clinical manifestation, diabetes mellitus is categorized in traditional Chinese medicine (TCM) as Xiao Ke, meaning wasting and thirsting disorder. The reference to diabetes by the traditional term appears as early as 475 BC, in the first medical text in Chinese history, Huang Di Nei Jing, or The Yellow Emperor's Inner Classic. The Characteristic features of Xiao Ke are excessive thirst, hunger, urination, emotional disturbance, an improper diet and eating habits, overindulgent sexual activity and dryness. Depending on the TCM pattern, Xiao Ke is classified into three levels. The upper level is characterized by the prominence of excessive thirst and a dry mouth, the middle level is characterized by the prominence of excessive hunger and the lower level is dominated by excessive urination and lumbar pain.

Diabetes mellitus is a heterogeneous endocritic disorder disease, characterized by the abnormal metabolism of carbohydrate, lipid and protein [1]. The long-term durative hyperglycemia usually concurs serious macrovascular and microangiopathy complications, which influence the patient's quality of life and leads to disabilities and high mortality [2-4]. Due to the rapid dietary and lifestyle alterations, the past two decades

Table 1. Existing chemical drugs and their molecular targets for Type 2 diabetes.

Drug class	Molecular target	Site of action	Adverse reactions
Insulin	Insulin receptor	Liver, muscle, fat	Hypoglycemia, weight gain
Sulphonylureas	SU receptor, K^+ ATP channel	Pancreatic β-cells	Hypoglycemia, weight gain
Biguanides	Not clear	Liver, muscle	Gastrointestinal disturbance, lactic acidosis
Acarbose	α-Glucosidase	Intestine	Gastrointestinal disturbance
Miglitol	α-Glucosidase	Intestine	Gastrointestinal disturbance
Thiazolidinediones	PPAR-γ	Fat, muscle, liver	Weight gain, edema, anemia
Exenatide	GLP-1 receptor	Pancreatic-α-cells, intestinal mucosa L-cells	Nausea, hypoglycemia, diarrhea vomiting
Pramlintide	Amylin receptors	NA, DVC	Nausea, hypoglycemia
Sitagliptin	DPP-IV	Intestine	Headache, nausea
Repaglinide	K^+ ATP channel	Pancreatic β-cells	Hypoglycemia, bellyache, nausea, vomiting, liver damage

DDP: Dipeptidyl peptidase; DVC: Dorsal vagal complex; GLP: Glucagon-like peptide-1; NA: Nucleus accumbens; PPAR: Peroxisome proliferator-activated receptor; SU: Sulphonylurea.

have seen an explosive worldwide increase in the number of people that are diagnosed with diabetes mellitus. It is estimated that the number of people with diabetes in the world is ~ 120 million now [101] and it will rise up to 300 million by 2010 [5]. Unfortunately, the presently available oral hypoglycemic agents and insulin therapy have limitations with regard to systemic efficacy, patient compliance and adverse effects, which have promoted a tremendous effort worldwide in searching for alternative therapeutic approaches for this metabolic disease. With thousands of years of practice, TCM has much to offer to diabetic patients, with its therapeutic modalities, including acupuncture, moxibustion, herbal medicine, massage, nutritional therapy, Tai Chi and other therapies. Prediabetes or early-stage diabetes can be treated solely with TCM, whereas moderate and severe cases are best treated with both TCM and chemical drugs [6,7]. The integration of TCM and allopathic drugs can lead to a better control of the disease, resulting in a decrease in drug dosage(s), the number of medications, side effects and minimize the effects of adverse reactions. It may also reduce diabetic complications [8,9].

2. The existing antidiabetic chemical drugs

Type 2 diabetes mellitus, which accounts for > 90% of all the diabetic patients in the world, is the consequence of a deficiency in the action of insulin due to abnormalities at the cell surface or within the cell, therefore resulting in a combination of defects in insulin secretion and/or action. Many oral antidiabetic agents are now available and are widely used for the management of Type 2 diabetic patients, with different modes of action and different types of side effects (**Table 1**).

The treatment of Type 2 diabetes using these chemical drugs is complicated by several factors inherent to the disease process, typically insulin resistance, hyperinsulinemia, hypertension, impaired insulin secretion and cholesterol abnormalities etc. As a result, the chemical drugs, when used individually, often have a limited therapeutic effect in maintaining a normal glucose and lipid metabolism as well as a number of conditions associated with diabetes. In fact, the use of several of these drugs in combination is sometimes able to provide improved glycemic control and overall treatment efficacy. Therefore, the multifactorial pathogenicity of diabetes demands a multimodal therapeutic approach. Thus, future therapeutic strategies require the combination of various types of antidiabetic agents, including a strategy to use multi-component-based natural products.

3. Effective compounds from nature products

With the scientific and technological development of natural product research, many effective compounds related to the management of diabetes mellitus have been isolated, purified and identified, including polysaccharides, alkaloids and flavones terpenoids etc. [10,11]. The therapeutic mechanisms of these active compounds have been investigated, which involve an increase in insulin sensitivity, the promotion of synthesis

of liver glycogen, decrease in decomposition of liver glycogen, enhancing glucose utilization in the peripheral tissue and protecting 13-cells in the pancreatic islets [12].

Cortex Moutan polysaccharide-2b (CMP-2b) is an active component that is isolated from *Paeonia suffruticosa*, with an average molecular weight of ~ 1.28×10^5 Da, which is a type of heterosaccharide consisting of rhamnose, arabinose, xylose, mannose, glucose and galactose. H Hong [13] reported that CMP-2b displayed

Table 2. The effects of CMP-2b on diabetic rats ($\bar{X} \pm s$).

Group (n = 10)	Control	Model	CMP-2b	Phenformin
Dose (mg/kg)	–	–	60	100
Body weight (g)	330.1 ± 31.2	375.9 ±28.1‡	366.3 ± 31.4	360.2 ± 29.9
Water intake (Ml/d)	18.9 ± 3.3	24.2 ± 5.0‡	21.3 ± 3.2§	20.4 ± 3.1§
Food intake (g/d)	24.3 ± 3.8	30.2 ± 6.1*	23.3 ± 6.2§	22.4 ± 6.0§
FBG (mmol/L)	5.6 ± 0.7	6.5 ± 1.0‡	5.7 ± 0.8§	5.6 ± 0.6§
Ins (mU/L)	31.2 ± 9.3	37.3 ± 14.8*	35.2 ± 5.7	33.6 ± 11.1§
Tch (mmol/L)	2.3 ± 0.5	2.9 ± 0.4*	2.4 ± 0.5§	2.4 ± 0.6§
TG (mmol/L)	1.58 ± 0.2	1.76 ± 0.2*	1.5 ± 0.1¶	1.6 ± 0.2§
ISI	-5.2 (1.0)	-5.5 (0.7)	-5.3 (0.9)	-5.3 (0.9)

*$p > 0.05$; ‡$p > 0.01$ versus control group; §$p > 0.05$; ¶$p > 0.01$ versus model group.
CMP-2b: Cortex Moutan polysaccharide-2b; FBG: Fasting blood glucose; FIN: Fasting insulin number; ISI = lg1/(FIN×FBS); Ins: Insulin; ISI: Insulin sensitivity index; Tch: Total cholesterol; TG: Triglyceride.

its activity by lowering the fasting blood glucose level as well as improving diabetic symptoms, such as decreasing food and water intake in Wister male diabetic rats induced with STZ and a high fat diet. Meanwhile, some serum biochemical indices, such as triglyceride (TG), total cholesterol (Tch), insulin level and insulin sensitivity index, were improved after 5 weeks, implying that CMP-2b might have improved insulin sensitivity and the activity of the insulin receptor. The statistical methods of the t and F test was used in the experiment and this data is summarized in **Table 2**.

Lycium barbarum polysaccharide (LBP-D) is an effective component that is extracted from the traditional Chinese herb *Lycium barbarum*. Acidic and neutral polysaccharides from the plant were first isolated by Ling Wang *et al*. [14] and, subsequently, evaluated in alloxan-induced diabetes mice for immune-regulative effects. The effects of LBP-D on lymphocytes proliferation, IL-1, IL-2 and T lymphocytes subpopulations were shown in **Table 3**, respectively. Experimental data were expressed by mice ($X \pm s$) and the t test was used to make a comparison with different groups [15]. LBP-D appeared to be remarkably active in enhancing the lymphocyte proliferation, upregulating the T lymphocyte subsets (especially $CD4^+$ [cluster of differentiation 4]), elevating the IL-1 and IL-2 levels and, therefore, restoring the immunnoregulatory functions of the alloxan-induced diabetes mice.

Berberine, an isoquinoline alkaloid with antibacterial and antiviral activities, also exhibited a good diabetic effect in various models [16]. Berberine is isolated from a variety of plants, such as *Coptis chinensis, Berberis aquifoliu*, and *Berberis ariatata*, among which *Coptis chinensis* is the most frequently used medicinal plant in a number of traditional recipes for the treatment of Xiaoke and its complications. For instance, *Coptis chinensis* is the main ingredient in Xiaoke-ling tablets and Jiangtang pills, which are discussed in sections 3.1 and 3.2 of this review. Recently, berberine has been used to treat diabetes clinically and achieved satisfactory results, with 70% of patients experiencing a symptomatic improvement [17]. Weiping Liu [18] reported the use of berberine tablets to treat 36 patients with Type 2 diabetes, whose fasting blood glucose level were measured after berberine tablets were orally administered at 3.0 g/d for 1 month. The fasting blood glucose level of 15 patients was lowered to 7.8 ± 0.4 mmol/L, approaching the normal level, from 10.0 ± 3.5 mmol/L. The molecular mechanism of action on the antidiabetic effect of berberine had not been elucidated until 2006 by Z Cheng and

colleagues who demonstrated that berberine stimulated glucose uptake in L6 myotubes [19]. In their work, berberine was found to stimulate glucose uptake in a time- and dose-dependent manner. The additional glucose uptake stimulated by berberine does not vary according to insulin concentration and cannot be affected by the phosphatidylinositol 3-kinase (PI3K) inhibitor. Therefore, berberine is believed to exert hypoglycemic effects by stimulating glucose uptake through the AMP-AMPK-p38 MAPK pathway, with little or no effect on insulin signaling pathways.

The therapeutic mechanism of these antidiabetic compounds of plant origin is probably single-target-based, similar to that of chemical drugs. To date, a great number of compounds isolated from plants, animals and marine organisms have been characterized and extensively evaluated for their therapeutic activities against diabetes. However, very few of them have advanced to controlled, double-blind and multi-centered clinical trials where high potency and low toxicity are generally required as a prerequisite. On the other hand, the combination formulae of TCM, containing multiple medicinal plants that have evolved through years of clinical practice, are still routinely used today by medical practitioners in an attempt to improve the overall therapeutic efficacy and reduce side effects. It appeared that the selection of herbal ingredients in many of these multi-component herbal formulae is proven to have a sound scientific basis through modern research and evaluation. The mechanism of action of most of these antidiabetic combination formulae is still unknown, although a multi-targeted approach through a synergistic interaction *in vivo* is generally assumed in the treatment. The most frequently used combination formulae and their ingredients for the clinical treatment of diabetes are summarized in Table 4 [20-44].

Table 3. The effects of LBP-D immunoregulation in alloxan-induced diabetic mice ($\bar{X} \pm s$).

Groups (n = 10)	Dose (mg/kg)	Absorption values at 570 nm				Percentage of positive cells among TLS (%)	
		TLP	SLP	IL-1	IL-2	$CD4^+$	$CD8^+$
Control	–	0.56 ± 0.07	0.53 ± 0.15	0.32 ± 0.02	0.47 ± 0.03	87.82 ± 1.04	74.34 ± 2.02
Model	–	0.29 ± 0.01‡	0.27 ± 0.01‡	0.11 ± 0.01‡	0.14 ± 0.138‡	65.15 ± 2.71‡	71.93 ± 1.16*
LBP-D(1)	200	0.41 ± 0.03§	0.39 ± 0.03§	0.14 ± 0.01§	0.44 ± 0.09§	79.85 ± 2.79¶	71.12 ± 2.08
LBP-D(2)	400	0.42 ± 0.03§	0.39 ± 0.02§	0.21 ± 0.01¶	0.48 ± 0.02§	80.83 ± 2.73¶	71.29 ± 2.25
LBP-D(3)	800	0.58 ± 0.06¶	0.36 ± 0.03§	0.29 ± 0.01§	0.48 ± 0.05§	81.64 ± 1.90¶	72.58 ± 2.09

*$p < 0.05$; ‡$p < 0.01$ versus control group; §$p < 0.05$; ¶$p < 0.01$ versus model group.
LBP-D: *Lycium barbarum* polysaccharide; SLP: Spleen lymphocyte proliferation; TLP: Thymus lymphocyte proliferation; TLS: T lymphocyte subpopulations.

4. Antidiabetic combination formulae of traditional Chinese medicine

4.1 Xiaoke-ling

Xiaoke-ling tablets and Jiangtang pills are two antidiabetic complex formulae embodied in the 2000 Chinese Pharma-copeia, edition I. Xiaoke-ling tablets, which are developed from a Xiaoke-ling decoction, the base formula, is widely used by TCM practitioners for the treatment of diabetic conditions. The formula consists of 10 medicinal herbs, *Rehmannia glutinosa, Schisandra chinensis, Ophiopogon japonicuc, Paeonia suffluticosa, Astragalus membranaceus, Coptis chinensis, Poria cocos, Panax ginseng, Trichosanthes kirilowii and Lycium barbarum. Among them, Rehmannia glutinosa* and *Ophiopogon japonicuc*, with the major ingredients being polysaccharides, are regarded as key components that exert the main therapeutic effect of the whole formula. *Rehmannia glutinosa* oligosaccharide (ROS) showed a significant hypoglycemic effect in Type 2 diabetic rats induced by streptozotocin (STZ). The antidiabetic mechanism of ROS was believed to be associated with an increase of the hepatic storage of glycogen and insulin levels and a decrease in glucose-6-phosphatase activity [45]. Polysaccharides from *Ophiopogon japonicuc* are believed to provide antidiabetic properties through the repairing of injured pancreatic islet 13-cells and facilitating the secretion of insulin [46]. *Schisandrae chinensis*, which is also regarded as an important component in the formula, is used to strengthen the effect of *Rehmannia glutinosa* and *Ophiopogon japonicuc* and, together, increases the overall symptomatic improvement for diabetic patients [47]. *Paeonia suffluticosa, Coptis chinensis* and *Trichosanthes kirilowii* are used to reduce the intrinsic

factors of thirst as well as promote blood circulation. *Astragalus membranaceus* and *Panax ginseng* are the two ingredients used to strengthen the resistance of exogenous stimuli and stress. *Astragalus* polysaccharide (APS) mitigates renal pathologic development in STZ-induced diabetic rats [48]. Panaxadiol saponins (PDS) from *Panax ginseng* were reported to decrease the blood glucose and improve the disorder of the serum lipid and insulin sensitivity in diabetic rats [49]. *Poria cocos* and *Lycium barbarum* are used to regulate blood circulation [50] and immune function [13], respectively. All of the 1 0 herbs combined as a whole treat diabetic mellitus through multiple modes of action to achieve a synergistic effect.

Table 4. The most frequently used complex recipes and their compositions for diabetes or its complications.

Chinese name	Ingredients
Ban Xia Xie Xin Tang	*Pinellia ternate, Codonopsis pilosula, Poria cocos, Atractylodes machocephala, Zingiber offcinale*
Bu Yang Huan Wu Tang	*Astragalus membranacens*, *Angelica sinensis*, *Prunus persica*, *Carthamus tinctorius*, *Ligusticum chuanxiong*, *Purariae lobata*, *Rehmannia glutinosa*, *Pheretima aspergillum*, *Alisma orientalis*
Er Ye Jiang Tang Tang	*Morus alba*, *Eriobotryae japonica*, *Coptis chinensis*, *Cornus officinalis*, *Polygonatum kingianum*
Gui Long Tang	*Cinnamomum cassia*, *Pheretima aspergillum*, *Astragalus membranaceus*, *Paeonia lactiflora*, *Spatholobus suberectus*, *Ligusticum chuanxiong*
Hua Yu Jiang Tang Tang	*Rehmannia glutinosa*, *Lycium barbarum*, *Ophiopogon japonicuc*, *Schisandrae chinensis*, *Atractylodes macrocephala*, *Cornus officinalis*, *Bombyx mori*, *Carthamus tinctorius*, *Ligusticum chuanxiong*, *Crataegus pinnatifida*, *Coptis chinensis*
Huo Xue Hua Yu Tang	*Atractylodes lancea*, *Citrus reticulate*, *Atractylodes macrocephala*, *Poria cocos*, *Paeonia lactiflora*, *Polygonatum kingianum*, *Alisma orientalis*, *Coix lacryma-jobi*, *Salvia miltiorrhiza*, *Pinellia ternata*, *Panax notoginseng*
Jia Wei Liu Wei Tang	*Astragalus membranacens*, *Salvia miltiorrhiza*, *Purariae lobata*, *Scrophularia ningpoensis*, *Atractylodes lancea*, *Dioscorea opposite*
Qi Gui Tang	*Astragalus membranacens*, *Cinnamomum cassia*, *Paeonia lactiflora*, *Gastrodia elata*, *Morus alba*, *Chaenomeles speciosa*
Ren Shen Jia Bai Hu Tang	*Glysum fibrosum, Anemarrhena asphodeloides, Glycyrrhiza uralensis, Panax ginseng*
Shen Qi Di Huang Tang	*Astragalus membranacens*, *Dioscorea opposite*, *Codonopsis pilosula*, *Rehmannia glutinosa*, *Poria cocos*, *Alisma orientalis*, *Cornus officinali*
Shen Qi Jiang Tang Tang	*Astragalus membranacens*, *Pseudostellaria heterophylla*, *Rehmannia glutinosa*, *Cornus officinalis*, *Dioscorea opposite*, *Polygonum multiflorum*, *Trichosanthes kirilowii*, *Ophiopogon japonicuc*, *Lycium barbarum*, *Alpinia oxyphylla*, *Scrophularia ningpoensis*, *Bombyx mori*
Xiao Ke Kang Tang	*Angelica sinensis*, *Ligusticum chuanxiong*, *Paeonia lactiflora*, *Purariae lobata*, *Cornus officinalis*, *Cyperus rotundus*, *Nelumbo nucifera*, *Litchi chinensis*, *Prunella vulgaris*, *Poria cocos*, *Atractylodes macrocephala*
Xiao Ke Ling Tang	*Rehmannia glutinosa*, *Schisandra chinensis*, *Ophiopogon japonicuc*, *Paeonia suffruticosa*, *Astragalus membranaceus*, *Coptis chinensis*, *Poria cocos*, *Panax ginseng*, *Trichosanthes kirilowii*, *Lycium barbarum*, *Pinellia ternata*, *Magnolia officinalis*, *Atractylodes macrocephala*, *Salvia miltiorrhiza*, *Leonurus japonicus*, *Paeonia lactiflora*
Yi Qi Yang Yin Tang 1	*Astragalus membranaceus*, *Panax quinguefolium*, *Dioscorea opposite*, *Scrophularia ningpoensis*, *Atractylodes lancea*, *Salvia miltiorrhiza*, *Purariae lobata*, *Codonopsis pilosula*, *Ophiopogon japonicuc*, *Schisandrae chinensis*, *Paeonia lactiflora*
Yi Qi Yang Yin Tang 2	*Pseudostellaria heterophylla*, *Astragalus membranaceu*, *Scrophularia ningpoensis*, *Rehmannia glutinosa*, *Coptis chinensis*, *Atractylodes lancea*, *Crataegus pinnatifida*
Yi Qi Hua Yu Tang	*Astragalus membranacens*, *Prunus persica*, *Carthamus tinctorius*, *Ligusticum chuanxiong*, *Salvia miltiorrhiza*, *Panax notoginseng*, *Rheum palmatum*, *Whitmania pigra*

Table 4. The most frequently used complex recipes and their compositions for diabetes or its complications (continued).

Chinese name	Ingredients
Zhu Shi Jiang Tang Tang	*Astragalus membranacens*, *Dioscorea opposite*, *Atractylodes lancea*, *Salvia miltiorrhiza*, *Purariae lobata*
Liu Wei Di Huang Wan	*Rehmannia glutinosa*, *Dioscorea opposite*, *Cornus officinalis*, *Paeonia suffruticos*, *Poria cocos*, *Alisma orientalis*
Yi Qi Yang Yin Huo Xue San	*Codonopsis piosula*, *Astragalus membranaceus*, *Poria cocos*, *Dioscorea opposite*, *Salvia miltiorrhiza*, *Leonurus japonicus*, *Atractylodes lancea*, *Atractylodes macrocephala*, *Purariae lobata*, *Glycyrrhiza uralensis*
Jian Pi Hua Yu Pian	*Panax ginseng*, *Astragalus membranaceus*, *Rehmannia glutinosa*, *Polygonum multiflorum*, *Atractylodes lancea*, *Scrophularia ningpoensis*, *Trichosanthes kirilowii*, *Artemisia scoparia*, *Coptis chinensis*, *Rheum palmatum*, *Salvia miltiorrhiza*, *Pheretima aspergillum*
Jin Qi Jiang Tang Pian	*Lonicera japonica*, *Astragalus membranaceus*, *Coptis chinensis*
Huang Lian Wan	*Coptis chinensis, Rehmannia glutinosa*
Jiang Tang Wan	*Astragalus membranaceus*, *Pseudostellaria heterophylla*, *Rehmannia glutinosa*, *Atractylodes lancea*, *Salvia miltiorrhiza*, *Purariae lobata*, *Lycopus lucidus*, *Whitmania pigra*, *Alisma orientalis*, *Pinellia ternata*, *Sargassum pallidum*
Shen Qi Wan	*Rehmannia glutinosa, Dioscorea oppasita, Cornus officinalis, Alisma orientalis, Poria cocos, Paeonia suffruticosa, Aconitum camichaeli*
Yu Quan Wan	*Panax ginseng, Astragalus membranaceus*, *Poria cocos, Prunus mume, Teichosanthes kirilowii, Pueraria lobata, Glycyrriza uralensis, Ophiopogon japonicus*

In the pharmacologic evaluation of Xiaoke-ling formula in an alloxan-induced rat model, the formula significantly decreased ($p < 0.01$) the blood glucose level and increased insulin level at a dose of 21.60 g/kg i.g., compared with those of a model group. Meanwhile, Xiaoke-ling treated rats showed a significantly improved histology of pancreatic islet and β-cell of pancreatic islet as compared with the no-treatment group. On the basis of these results, Xiaoke-ling is likely to be able to protect pancreatic cells, help repair and restore the function of the β cells of the pancreatic islet and thus increase insulin secretion [51]. A clinical evaluation of Xiaoke-ling was also conducted with 312 Type 2 diabetic patients at the People's Hospital of Taiyuan, Shanxi province [52]. Of all the patients evaluated, 118 individuals achieved a marked therapeutic effect (main clinical symptoms were recovered and the average fasting blood glucose level was < 6.66 mmol/L) and 181 showed an improvement (main clinical symptoms were significantly improved and the average fasting blood glucose level was < 8.25 mmol/L).

4.2 Jiangtang (sugar lowering) pill

Jiangtang pill, another clinically important hypoglycemic formula documented in the Chinese Pharmacopeia, consists of *Panax ginseng, Astragalus membranaceus, Polygonatum kingianum, Poria cocos, Atractylodes macrocephala, Purariae lobata, Schisandrae chinensis, Coptis chinensis, Rheum palmatum, Glycyrrhiza uralensis.* The formula is similar to Xiaoke-ling in its components. It was reported that polygona polysaccharose decreases the expression of the receptor of glycosylated end product (RGEP) mRNA in the brain tissue in aged diabetic rats and has a protective effect on the tissue damage caused by hyperglycemia and advanced glycosylated end products (AGE) [53]. Astragalus membranaceus polysaccharide-B (AMP-B) is found to significantly decrease the consumption of water and food, reduce the pancreatic damage and inhibit the atrophy of thymus and pancreas tissues in the alloxan-induced diabetic rats [54]. Puerarin, an active compound from *Purariae lobata*, displays the hypoglycemic effect by increasing the content of glucose transporter-4 (GLUT4) protein in adipocytes of STZ-diabetic rats [55]. Chunxiu Chen *et al*. reported that the Jiangtang pill significantly ($p < 0.05$) decreased blood glucose level at a dose of 35.6 g/kg via oral administration in the alloxan-induced diabetic rat model. The total water intake and urine volume of the treated rats were reduced by 32.6 and 31.5%, respectively. The TG, Tch and blood urea nitrogen levels decreased remarkably [56] in the treatment group ($p < 0.05$). These positive results were further validated in a clinical trial for a 6-month consecutive administration of the pills four times per day, where the diabetic symptoms of 35 patients of 164

cases improved, fasting blood glucose levels were maintained < 7.2 mmol/L, postprandial hyperglycemia < 8.3 mmol/L, whereas 69 patients experienced a moderate improvement [57].

4.3 Jianpi Huayu tablets

Instead of traditional preparations of TCM, such as decoction, syrup (spherical), pills, some antidiabetic formulae have been prepared into more convenient dosage forms such as capsules, granules and tablets, which have all been well received by the market. One of these preparations is the Jianpi Huayu tablet, which consists of *Panax ginseng, Astragalus membranaceus, Rehmannia glutinosa, Polygonum multiflorum, Atractylodes lancea, Scrophularia ningpoensis, Trichosanthes kirilowii, Artemisia scoparia, Coptis chinensis, Rheum palmatum, Salvia miltiorrhiza* and *Pheretima aspergillum*. The therapeutic effects of Jianpi Huayu tablets for the management of diabetes with insulin resistance were observed in the Chinese medicine hospital of Jinan in the Shandong province [58]. Chenqin Liu *et al*. conducted a clinical trial for the 8-week consecutive administration of the tablets 3 times per day to 65 patients with Type 2 diabetes. A total of 8 patients exhibited a significant improvement in diabetic symptoms, in which fasting blood glucose levels were maintained < 7.2 mmol/L, postprandial hyperglycemia less than 8.3 mmol/L, although 45 patients experienced moderate improvement and 12 patients had no effect.

4.4 Single-herb formulae used for diabetes

About 187 kinds of traditional Chinese herbs have been documented in the Compendium of Material Medica that have antidiabetic effects. Recently, several of these medicinal herbs with unique phytochemic ingredients and hypoglycemic potency have attracted investigators, one of which is *Rheum officinale*. Cuiling Huang *et al*. reported that the levels of prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) and thrombaxane B_2 (TXB_2) in the renal cortex and urine were distinctly decreased, whereas P/T ($PGF_{1\alpha}/TXB_2$) was markedly increased, close to normal levels when the diabetic rats were treated with the ethanol extract (1g/kg) of *Rheum officinale*. Furthermore, the activities of superoxide dismutase (SOD) and catalase (CAT) were significantly elevated, but the lactoperoxidase (LPO) concentration in the kidneys and urine were markedly lowered. These results clearly implied that the ethanol extract of *Rheum officinale* was beneficial for diabetic nephropathy and likely to be considered to be a candidate for this diabetic complication [59].

Ginseng is a well-known invigorator that can effectively strengthen the systemic regulatory network in response to interior and exterior stimuli [60]. Various extracts from ginseng roots, fruits and entire plants have been reported to be beneficial for diabetes mellitus [61]. Additionally, ginsenoside Re (a major compound of ginseng) was recently reported to alter the expression of serum protein in diabetic rats [62]. The protein was further determined as C-reactive protein (CRP), a kind of cytokine involved in the process of inflammation. Therefore, ginsenoside Re might alleviate the inflammatory conditions associated with insulin resistance. A total of 18 frequently used herbs in TCM are listed in **Table 5**, in which the water extract of herbs is the predominant form that is used for clinical treatment of diabetes.

5. Conclusion

There is no doubt that the terrestrial plants used in traditional Chinese medicine may provide the raw materials/lead molecules for antidiabetic drugs. A multitude of herbs, spices and combination herbal formulae are being used in the management of diabetes mellitus with a relatively insufficient knowledge of their mechanism of action as well as adverse effects and safety profiles. About 187 different Chinese medicinal herbs, along with combination formulae, are clinically applied to treat diabetes mellitus and its complications in China, most of which have achieved reasonably good clinical outcomes. This valuable data and practical experience provides a promising opportunity for the discovery and development of drug candidates with good therapeutic efficacy and low toxicity.

Multiple chemical drugs have been used in compound formula, such as combination metformin and sulfonylurea, insulin and metformin, to treat diabetes or its complications clinically by western medicine and yielded better effects than the use of a single drug. TCM is usually used in this way as a multi-component

Table 5. The most frequently used single recipes for the treatment of diabetes or its complications.

Chinese names	Binomial names	Medicinal position names
Chuanxiong	*Ligusticum chuanxiong*	Rhizoma Chuangxiong
Dahuang	*Rheum palmatum*	Radix et Rhizoma Rhei
Danshen	*Salvia miltiorrhiza*	Radix Salviae miltiorrhizae
Dongchong xiacao	*Cordyceps sinensis*	Cordyceps
Fuling	*Poria cocos*	Poria
Gouqizi	*Lycium barbarum*	Fructys Lycii
Heshouwu	*Polygonum multiflorum*	Radix Polygoni Multiflori
Huangliang	*Coptis chinensis*	Rhizoma Coptidis
Huangqi	*Astragalus membranacens*	Radix Astragali
Huangqin	*Scutellaria baicalensis*	Radix Scutellariae
Luohanguo	*Momordica grosvenori*	Fructus Momordicae
Maidong	*Ophiopogon japonicus*	Radix Ophiopgonis
Niubangzi	*Arctium Lappa*	Fructus Arctii
Renshen	*Panax ginseng*	Radix Ginseng
Sangzhi	*Morus alla*	Ramulus Mori
Tianhuafen	*Trichosanthes kirilowii*	Radix Trichosanthis
Wubeizi	*Melaphis chinensis*	Galla Chinensis
Wuweizi	*Schisandra chinensis*	Fructus Schisandrae Chinensis

therapeutic approach by medical practitioners, including single-herb formulae, which contain multiple phytochemical compounds, and combination herbal formulae. This shall be regarded as a concerted pharmacologic intervention of multiple compounds interacting with multiple targets and possessing interdependent activities that are required for a synergistic or optimal effect. The interaction between the ingredients in a multi-component herbal formula and the diseased state of the host might be far more complex than merely the result of a direct interaction that is exerted by a single chemical entity. Therefore, the conventional approach of the discovery and development of antidiabetic drug products, which is mainly on the basis of bioactivity guided single compound screening from thousands of herbs, has proven to be a non-productive direction. With modern sciences and emerging technologies, such as systems biology, multi-disciplinary approaches have been widely applied to study complex metabolic diseases, including diabetes mellitus. Recently, systems biology approaches, including genomics, proteomics and metabonomics, have been extensively applied to elucidate the mechanism of antidiabetic effects [63-65]. The authors' knowledge from drug discovery and development with single compound therapeutic agents and multi-component herbal agents has provided a unique overlap that may evolve a new approach for diabetes mellitus drug discovery and development. That is, multiple compounds with known structures and compositions, such as flavonoids, alkaloids and polysaccharides, extracted from a well-organized, therapeutically effective combination formulae, are to be combined, under the guidance of pharmacologic evaluation, to maximize their efficacy and minimize toxicity and to achieve an optimal therapeutic goal for diabetes mellitus.

6. Expert opinion

Based on the conclusions stated previously, the authors think that the discovery and development of new antidiabetic drugs from nature Chinese herbal products should be guided by the theory of traditional Chinese medicine, which takes a holistic view on diabetic conditions and the personalized treatment. Multi-component herbal medicines may be advantageous in that several active ingredients of different types in combination, such as flavonoids, alkaloids and polysaccharides, may provide a synergistic effect through multi-layer interactions *in vivo* with multiple targets associated with a hyperglycemic condition. An alternative way of developing new antidiabetic drug candidates is to simplify an existing herbal formula with demonstrated clinical efficacy, under the guidance of pharmacologic evaluation, to finally obtain a group of several phytochemic compounds that are as

therapeutically effective as the original formula and has known chemical structures, compositions and mechanism of action, similar to chemical drugs.

The dynamic nature of biology is not easily modeled and the treatment of a complex, multifactorial metabolic disease, such as diabetes, using multi-component therapeutics is more difficult to model. The concept of a linear drug discovery and development spectrum will be gradually replaced by an iterative process, where the knowledge gained by a systems biology approach is applied at various points in a continuum. Combination herbal formulae and combination phytochemic compounds derived from traditional formulae with a holistic therapeutic approach may hold the potential to become the therapeutics of choice in the future, due to the synergistic effect and dynamic adjustment achieved by the multiple ingredients that inhibit the causative factors at different stages, strengthen the impaired immune system and improve the overall symptoms and the patient's quality of life.

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